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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
LEFFERS JR,G	
ART UNIT	**PAPER NUMBER**
1626	7

DATE MAILED: 10/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/342,024	NOLAN ET AL.
	Examiner	Art Unit
	Gerald Leffers	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-29 is/are pending in the application.

4a) Of the above claim(s) 3,13-16,18 and 23-29 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4-12,17, and 19-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other. .

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-2, 4-12, 17, 19-22, drawn to in vivo methods of introducing a nucleic acid into a cell, classified in class 514, subclass 44; class 435, subclass 461.

II. Claims 1, 3-22, drawn to in vitro methods of introducing a nucleic acid into a cell, classified in class 435, subclass 461.

III. Claims 23-24, 26-29, drawn to in vivo methods for introducing a polypeptide into a cell, classified in class 604, subclass 501.

IV. Claims 23, 25-29, drawn to in vitro methods for introducing a polypeptide into a cell, classified in class 435, subclass 173.6.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I-IV are biologically and functionally different and distinct from each other and thus one does not render the other obvious. The methods of Groups I-IV comprise steps which are not required for or present in the methods of the other groups: application of an electrophoretic field to nucleic acid/cell mixture wherein the cell is located in an organism (Group I), application of an electrophoretic field to nucleic acid/cell mixture in vitro (Group II); application of an electrophoretic field to polypeptide/cell mixture wherein the cell is located in an organism (Group III) and application of an electrophoretic field to polypeptide/cell mixture in vitro (Group IV). The end result of the different methods are different: introduction of a nucleic acid into a cell in an organism (Group I), introduction of a nucleic acid into a cell in

solution (Group II), introduction of a polypeptide into a cell in an organism (Group III) and introduction of a polypeptide into a cell in vitro (Group IV). Thus, the operation, function and effects of these different methods are different and distinct from each other. Therefore, the inventions of these different, distinct groups are capable of supporting separate patents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and because the non-patent literature search required for each group is different (e.g. in vivo versus in vitro electroporation; nucleic acid compositions versus polypeptide compositions for electroporation) restriction for examination purposes as indicated is proper.

During a telephone conversation with Lisa Haile on 9/24/01 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-2, 4-12, 17, 19-22. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3, 13-16, 18 and 23-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-12, 17, 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of the claims is drawn towards a method for introducing nucleic acid into a cell in vivo wherein a "low" electrical field impulse is applied to a cell for a "long pulse length" after contacting the cell with the nucleic acid. Each of the claims comprises the functional limitation of "...wherein the impulse is of sufficient duration and strength to introduce the nucleic acid into the cell...". Specific embodiments of the claims are drawn towards specific parameters for field strength (e.g. 300-600 V/cm), electrical pulse duration (e.g. 10-100 milliseconds) or temperature (e.g. 37°C). Other claimed embodiments are directed towards specific cell types (e.g. stoma, hematopoietic, dividing or nondividing). The claims embrace a broad genus of potential combinations of nucleic acid composition/tissue-organism/electrode set-up/electrical field-pulse duration-pulse frequency.

The specification provides a very brief description of how nucleic acids can be delivered *in vivo* (e.g. intravenously, transdermally, etc.), but provides no further description other than to state that it is preferred that the site of electroporation be "at or near" the site of delivery. Various compositions for delivery of the nucleic acid are provided (e.g. sterile aqueous solutions, Ringers solution, etc.), although not in the context of any particular in vivo embodiment of the invention. A single working example is provided in the specification which is directed at an *in vitro* embodiment of applicants' invention wherein a human long-term bone marrow cell culture is transformed with a nucleic acid encoding a green fluorescent protein marker (GFP) by electroporation. No description is provided in the specification for any electrode system to be used to practice in vivo embodiments of the invention (e.g. type of electrodes, mode of application to the subject organism, appropriate DNA composition for a given electrode/tissue combination). No description is provided for any combination of electrodes and tissue in a test subject (e.g. for electroporation of skeletal muscle of the rat or electroporation of hematopoietic stromal cells in humans, etc.). There is no basis provided by the specification for one of skill in the art to envision a representative number of specific embodiments of the claimed in vivo methods sufficient to describe the broadly claimed genus.

While the prior art does provide a limited number of examples wherein nucleic acids are transformed into cells in vivo by electroporation, relatively few appear to describe embodiments practiced with the specific "low" electronic field strength and "long" impulse duration of the instant invention. There does not appear to be any description in the prior art of in vivo electroporation of hematopoietic or hematopoietic stromal cells with nucleic acids. The few examples provided in the art do not provide a basis for one of skill in the art to envision a

representative number of electrode set-up/pulse conditions/tissue combinations embraced by the rejected claims.

Given that the specification provides almost no description of in vivo embodiments of the claimed invention and that the prior art does not adequately compensate for the descriptive deficiencies of the specification (e.g. electrode set-up for a given tissue in a given organism, etc.), one of skill in the art would not have been able to envisage a representative number of embodiments of the claimed invention sufficient to describe the broad genus of in vivo electroporation methods embraced by the rejected claims. Therefore, one of skill in the art would reasonably conclude applicants were not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-12, 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that it is drawn towards nonelected embodiments of the invention. It would be remedial to amend the claim language to specify that the electroporation is practiced in vivo.

Claim 1 is vague and indefinite in that the metes and bounds of the phrase "...a low electrical field impulse..." are unclear. The term does not appear to be well defined in the specification. While preferred embodiments are described in the specification, no boundary limits for what constitutes a "low" electrical field impulse are provided. It would be remedial to

amend the claim language to more clearly indicate what is intended as a "low" electrical field impulse.

Claim 1 is also vague and indefinite in that the metes and bounds of the term "long pulse length" are unclear. Again, boundary limits for what constitutes a "long" pulse length are not defined in the specification. It would be remedial to amend the specification to more clearly indicate the limitations intended by the term "long pulse length".

Claim 8 is vague and indefinite in that the metes and bounds of the term "limited duration" are unclear. The term does not appear to be defined in the specification. It is unclear what length of time for a particular wave form would constitute a "limited" duration. It would be remedial to amend the claim language to more clearly indicate the length of time which would constitute a "limited" duration.

Claims 19-22 are vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the cells" in claim 1, upon which these claims are dependent. It would be remedial to either amend claim 1 to provide antecedent basis for the term or amend the term to read "the cell".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-2, 4-11, 19-20 rejected under 35 U.S.C. 102(e) as being anticipated by Dev et al (U.S. Patent No. 5,944,710; see the entire patent).

The Dev et al patent (the '710 patent) teaches compositions and methods for the sustained intravascular delivery via electroporation of therapeutic compositions (Abstract). The therapeutic compositions of the invention include nucleic acids such as plasmids or anti-sense oligonucleotides against c-myc or c-myb (column 3, line 21; column 5, lines 15-21). The electric fields needed for in vivo cell electroporation according to the invention can ranger from 100V/cm to several kV/cm (column 10, lines 1-9). The waveforms of the voltage pulse provided by the generator in the power pack can be exponentially decaying pulse, square pulse, unipolar oscillating pulse train or bipolar oscillating pulse train (column 10, lines 55-60) The pulse length can be 100 microseconds to 100 milliseconds, preferably from about 500 microseconds to 10 milliseconds. From about 1 to 10 pulses can be applied to an area or group of cells (column 11, lines 5-10). A gene transfer experiment is exemplified wherein a standard marker gene, lacZ driven by a CMV promoter, was infected into an artery followed by electroporation (three pulses at 10 second intervals at 76 V and .76 milliseconds) (column 14, lines 15-49

Claims 1-2, 4-11, 19-20 are rejected under 35 U.S.C. 102(e) as being anticipate by Dev et al (U.S. Patent No. 5,859,327; see the entire patent).

The Dev et al patent (the '327 patent) teaches methods for producing genetically altered plants by introducing a polynucleotide to an intact plant or plant cells by electroporation (e.g. Abstract). The '327 patent teaches that a large number of nucleic acid types, including plasmid

DNAs, can be used in the invention (columns 4-6; column 6-lines 34-44). The wave pulse can be square wave pulses, exponential waves, unipolar oscillating wave forms of limited duration, bipolar oscillating wave forms of limited duration or other wave forms generating electric fields (column 7, lines 63-67). The number of pulses sufficient to cause electroporation ranger from 1 to 100, preferably between 1 to 50 (column 8, lines 34-37). The patent teaches that one of skill in the art could determine the appropriate parameters for the leaf type used. For example, "soft and thin" leaves such as petunia are electroporated at low voltage and long pulse length (e.g. 40-50 V/cm and 50 ms, respectively). Typically, the electric field strength of the electrical impulse applied is from about 1 to 30 kV/cm. The pulse length is from about 1 microsecond to 20 milliseconds (column 8, lines 35-67). The patent teaches methods for electroporation of intact plants or for leaf sections harvested from plants (e.g. Figures 1 and 3; Example 3).

Claims 1-2, 4-12, 19-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamazaki et al (Biology of Reproduction, December 1998, Vol. 59, pages 1439-1444; see the entire reference).

Yamazuki et al teach a method for in vivo gene transfer to mouse spermatogenic cells comprising DNA injection into seminiferous tubules and subsequence electroporation. The authors teach their method provides a convenient assay for gene expression during spermatogenesis (i.e. expression in dividing cells). The 2 month duration of marker expression is some cell types indicate that spermatogenic stem cells (i.e. nondividing cells) and/or spermatogonia could also incorporate foreign DNA and that the transgene could be transmitted to progenitor cells derived from transfected germ cells (Abstract). The electroporation methods

of the invention comprised intratubular or interstitial injection of Qiagen Maxi column-purified plasmid DNAs into the testes followed by electroporation. The electroporation conditions comprised holding the testes between tweezer-type electrodes and application of square electric pulses eight times at 20-50 V with a constant time of 50 milliseconds (page 1440, in vivo EP paragraph). One of skill in the art would necessarily conclude upon reading the teachings of Yamazuki et al that the electronic field pulse used constitutes a "low" electronic field pulse and that the 50 millisecond pulse duration constitutes a "long duration". For example, the testes shown in Figure 1 are ~2-3 mm in diameter, indicating a gap of ~.2-.3 cm and a probable field strength of ~250 V/cm. It is noted that the relative term "about" is not clearly defined in relation to field strength or electronic pulse duration (e.g. "about" 300-600 V/cm or "about" 10 to 100 milliseconds).

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers , Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Rob Schwartzman, Ph.D., can be reached at (703) 308-7307.

Any inquiry of a general nature or relating to the status of this application, or relating to attachments to this office action, should be directed to the Patent Analyst Zeta Adams, whose telephone number is (703) 305-3291.

GLJ

G. Leffers Jr., Ph.D.
Patent Examiner
Art Unit 1636
September 27, 2001

PRIMARY EXAMINER